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Pellet characteristics and drug release when the form of propranolol is fixed as moles or mass in formulations for extruded and spheronized Carbopol-containing pellets

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ABSTRACT

Characteristics of Carbopol-containing pellets have been shown to be dependent on the form of the weakly basic drug, propranolol, when the drug forms are fixed as masses in the formulations. To further investigate the effect of the drug forms on pellet and drug release characteristics, the drug forms were incorporated as a fixed number of moles in the formulation. Forms of propranolol, viz. the free base and the hydrochloride and maleate salt forms, resulted in different yield, roundness, smoothness, and friability, but the average pellet diameter was not affected. The free base form was released more slowly than the other two forms. Mathematical analysis of the release data revealed that Fickian diffusion and polymer relaxation contributed to the release mechanism in each case, although polymer relaxation was more influential with the free base form.

1. Introduction

Extrusion–spheronization has become a widely used method for the production of pellets in the pharmaceutical industry (Vervaet et al., 1995). It offers manufacture of multiple unit dosage forms (Elchidana and Deshpande, 1999; Kojima and Nakagami, 2002; Liu et al., 2003; Abbaspour et al., 2005; Sungthongjeen et al., 2006) where the drug release and/or pellet characteristics can be modified as desired (Gandhi et al., 1999; Efentakis et al., 2000). The use of different polymers in extrusion–spheronization has been investigated extensively since polymers can contribute to the drug release by different release mechanisms (Pillai and Panchagnula, 2001; Abbaspour et al., 2005; Gandhi et al., 2005).

Carbopol is a polymer that influences drug release by allowing only diffusion through its matrix or by a swelling and gelling mechanism, depending on the pH conditions (Noveon, 2002). Carbopol® 974P, a pharmaceutical grade of this polymer, is composed of poly(acrylic acid) with the highest crosslinking density in the Carbopol family (Noveon, 2002). When wetted, Carbopol causes tack problems due to deprotonation of at least some of its carboxylic acid groups. This causes handling difficulties, lowers the yield, and reduces pellet roundness (Mezreb et al., 2004). Calcium chloride incorporation into the formulations can essentially eliminate the tack problem (Neau et al., 1996, 2000; Gomez-Carracedo et al., 2001). Because Carbopol is pH-sensitive, becoming anionic even at a pH as low as 4.0 (Nakanishi et al., 1998), the pH of the microenvironment (Bommareddy et al., 2006; Badawy and Hussain, 2007), the presence of other ions in the microenvironment (Bommareddy et al., 2006; Badawy and Hussain, 2007), the solubility of the drug (Vilches et al., 2002; Badawy and Hussain, 2007), and the cationic/non-ionic nature of the drug (Bommareddy et al., 2006) might affect the drug release rate and/or pellet characteristics.

In order to gain further insight into these effects, a study was conducted recently (Paker-Leggs and Neau, 2008) with different forms of propranolol, namely the free base, as well as the hydrochloride and maleate salt forms, incorporated into Avicel PH 101 pellets that contained 20% Carbopol® 974P. Suspected influences on the drug release included pH effects by the drug form and ionic strength effects due to the counterion of the propranolol salt form, as well as the effects of the calcium chloride that was included as a means to reduce the tack of wetted Carbopol. The ability of the hydrated Carbopol to swell and gel was influenced by pH and ionic effects, in particular by the free base and maleate forms. The large difference in the solubility of the salt forms was not reflected as a profound difference in drug release rates. However, the low solubility of the free base form was described as the most influential property that affected its release rate. The moving front, as well as the hydration and dissolution layer (Fig. 1), were considered the regions where hydration and/or dissolution of the hydrophilic substances took place. The gel layer was formed by the

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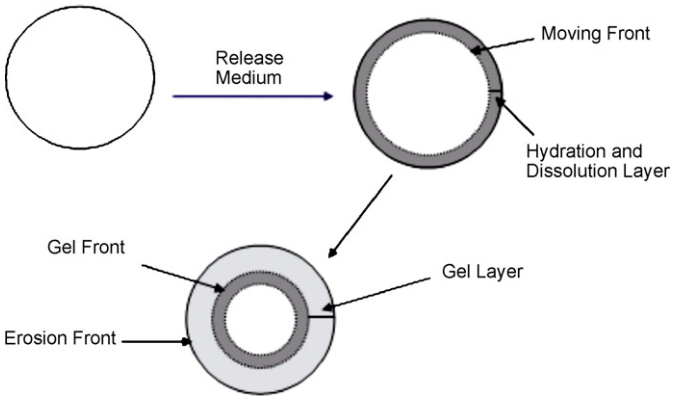

Fig. 1. A diagram showing the generation of the different fronts and regions of the hydrating, swelling, gelling, and drug releasing pellet.

repulsion of the carboxylate groups of Carbopol (Carbopol Resins Handbook, 1993) and this gel can hold a tremendous amount of release medium (Colombo et al., 2000; Islam et al., 2004).

Different pellet characteristics were obtained in that study (Paker-Leggs and Neau, 2008) that were also likely due to differences in the properties of the propranolol forms. The propranolol free base batch provided the lowest yield, smallest pellet size, highest roundness scores, and smoothest surfaces. This was attributed to the encouragement of the gel formation of Carbopol by the dissolved propranolol free base.

Because the amounts of the drug forms were fixed in all batches, the free base pellets had the greatest number of moles of propranolol, whereas propranolol maleate pellets had the least. Therefore, there was a concern that drug loading also contributed to the results. If the drug forms are fixed as moles instead of masses in the formulations, observable differences can be investigated further. Also, in the previous study, calcium chloride was used at a low concentration so that the tack would be reduced to the point where there were little handling difficulties. Therefore, the effect of calcium on the drug release was difficult to investigate because low concentrations of calcium in the release vessels would have been difficult to assay reliably. Although it is feasible to manufacture pellets without calcium when Carbopol® 974P is less than 20% of the pellet formulations (Mezreb et al., 2004), it is evident that calcium incorporation into the formulation improves pellet characteristics, especially in terms of roundness (Neau et al., 1996). The effect of calcium on the pellet characteristics and drug release rate can be investigated by increasing the amount to an optimal extent to eliminate tack completely (Neau et al., 1996).

The objective of this study was to further examine the drug release and pellet characteristics when the drug forms are fixed as moles and masses in the formulation. The effect of a higher calcium level on the drug release rate and pellet characteristics was also investigated. In addition to studying calcium release, drug release, and pellet characterization, possible interactions taking place at the moving front, in the hydration and dissolution layer, and in the gel layer were addressed and simulated experimentally.

2. Materials and methods

2.1. Materials

Propranolol hydrochloride (Fisher Scientific, Pittsburgh, PA) was used as the model drug. Sodium hydroxide (Sigma–Aldrich, St. Louis, MO) increased the pH during propranolol free base synthesis and in the preparation of the release medium. Methyl tert-butyl ether (MTBE, Fisher Scientific), tetrahydrofuran (THF, Sigma–Aldrich), and maleic acid (Fisher Scientific) were used in propranolol maleate synthesis. Calcium chloride dihydrate (Fisher Scientific) was used to reduce the tack in the pellet formulations. Potassium phosphate monobasic (Sigma–Aldrich) was used to prepare buffer solutions. A 1000 ppm calcium individual certified cation standard (Fisher Scientific) was used to prepare standard curves for the calcium release studies. Carbopol® 974P from Lubrizol Inc. (Cleveland, OH) and Avicel PH 101 from FMC Corporation (Philadelphia, PA) were used as the polymer studied and as the diluent, respectively. A Nanopure water system (Barnstead, Dubuque, IA) provided ultrapure water for use throughout the experiments.

2.2. Propranolol free base and propranolol maleate synthesis

The free base form of propranolol (PF) was synthesized as described in a previous study (Paker-Leggs and Neau, 2008). Briefly, propranolol hydrochloride (PH) was dissolved in water and, with vigorous stirring, the pH was gradually increased by the slow addition of sodium hydroxide solution to cause precipitation of PF. Propranolol maleate (PM) synthesis was accomplished by a method described by Brown (1998). Equal moles of PF and maleic acid were dissolved in warmed THF. MTBE was added as a non-solvent to cause precipitation of the PM salt. To find the purity of PF and PM, differential scanning calorimetry (DSC) studies, using a DSC 2910 (TA Instruments, New Castle, DE), were performed. UV analysis was accomplished using a Shimadzu (Columbia, MD) UV-1601 UV–visible spectrophotometer at a wavelength of 288 nm to back-calculate and verify the purity of these forms of propranolol.

2.3. Microenvironmental pH estimation

To each vial containing a 1 g sample of a pellet batch, 5 ml of pH 6.8 0.05 M phosphate buffer was added. The solution was stirred with a magnetic stirrer at a speed of 60 rpm. Starting from the first minute, the pH was recorded every minute up to 20 min using an Accumet Model AB15 Basic pH meter (Fisher Scientific). The pH was plotted as a function of time for each drug form. A change in pH should be due to the hydrating and/or dissolving components of the pellets, which would reflect pH effects at the moving front. All pH measurements were performed in triplicate at room temperature.

2.4. Precipitation of Carbopol-drug complexes

Preliminary studies revealed that near neutral phosphate-buffered Carbopol dispersions cause precipitate to form when mixed with propranolol solutions in the same medium. For each propranolol form, 40 ml solutions were prepared such that the addition of 10 ml of 0.2% Carbopol® 974P would bring the drug concentration to 3, 4, 5, 6, 7, or 8 mM. The pH was measured before and after the precipitation to ensure that it was above 6.4, such that carboxylate groups of Carbopol were formed and maintained. The drug concentration in the solution, after filtration of the precipitate with a 0.22 μm filter and then appropriate dilution, was measured using the UV–visible spectrophotometer. The differences between the control and the remaining concentrations were used to calculate the drug amount in the precipitate. Differences in the amount of drug in the precipitate could be attributed to the presence of miscellaneous ions offered by the drug form. Miscellaneous ions would interfere with the interaction between carboxylate groups of Carbopol and protonated propranolol such that less drug would form a complex. The potential for ionic interference with this interaction in the gel layer is even greater because the drug and Carbopol content would be higher than used in the complexation studies. Experiments for each drug form were performed in triplicate.

2.5. Manufacture of pellets

The powder blend mass for each batch of pellets was 300 g. Five different formulations were prepared in order to study each form present at a particular mass or as a particular number of moles. To fix the mass of drug in the formulation, the powder blend consisted of 5% of the particular propranolol form, 20% Carbopol, and 75% Avicel. In order to fix the three forms at a particular number of moles, the 5% mass for PF was converted to moles, and then the masses corresponding to the same number of moles of PH and PM were calculated. The mass of Avicel in the formulation was reduced to account for the extra drug mass such that the powder blend mass was maintained at 300 g. Therefore, the formulation for the propranolol HCl in moles, designated PH (mole), consisted of 5.70% PH, 20% Carbopol, and 74.30% Avicel. The formulation for propranolol maleate fixed as moles, designated PM (mole), consisted of 7.24% PM, 20% Carbopol, and 72.76% Avicel.

The powders were mixed in a KitchenAid Model K5SS planetary mixer (Hobart Corporation, Troy, OH) for 10 min. Every 5 min, the mixer was stopped to scrape the walls of the mixer bowl and to mix manually any material found below the blade at the bottom of the bowl. Calcium chloride dihydrate was added as an aqueous solution, which was used as the wetting fluid, in order to reduce the tack that was generated by the carboxylate groups of Carbopol in the wetted mass (Neau et al., 2000; Bommareddy et al., 2006). The amounts of calcium chloride dihydrate and water were based on the equations presented by Neau et al. (2000). After calcium chloride was dissolved in distilled de-ionized water, the solution was slowly introduced to the powder blend by a syringe while the blend was still being mixed. The wetted mass was immediately fed into a Model EXDS-60 radial twin-screw extruder (Fuji Denki Kogyo Company, Osaka, Japan) with a 1.5 mm screen at a speed of 20 rpm. The extrudates were immediately transferred into a Q230 Marumerizer (Fuji Denki Kogyo Company), which included a cross-hatched groove pattern plate, operated at a speed of 860 rpm for 10 min. The pellets were air-dried for 2 h, and then oven dried at 40 °C at least overnight.

2.6. Pellet characterization

Using an HB43 halogen moisture analyzer (Mettler Toledo, Columbus, OH), moisture analysis was performed in triplicate. For each batch of pellets, a sample of approximately 1 g was accurately weighed and then heated to and maintained at 105 °C. The mass was recorded every 5 min to ensure that the mass was consistent at 10 and 15 min. The moisture content, calculated as the difference between the initial mass and the mass at 15 min divided by the initial mass, was expressed as a percentage.

Sieve analysis was performed using a nest of U.S. Standard Sieves between Nos. 8 and 35. The average diameter was calculated using the equation below:

$$d_{\text{avg}} = \frac{\sum \text{MO} \times \%\,\text{retained}}{100\%} \quad (1)$$

where MO is defined as the mean sieve opening for each sequential pair of sieves in the nest of sieves. % Retained is the mass of pellets retained on the sieve in that pair that has the smaller aperture, expressed as a percentage of the total mass of pellets in the sieve analysis. The entire mass of each bead batch experienced sieve analysis. Yield is defined as the percentage of pellets found in the 14/20 meshcut. Only the pellets in this meshcut were used in further studies to minimize pellet size effects on characteristics.

A 1 g pellet sample and twenty-five 3 mm glass beads were placed in a Model DF-1W friabilator (Distek, North Brunswick, NJ). The friabilator was allowed to rotate 100 times at a speed of 25 rpm. After removal of the glass beads, the mass in the friabilator was sieved with a No. 20 sieve and weighed. The difference between the initial and final mass of the sample, divided by the initial mass and then expressed as a percentage, was reported as the friability.

The roundness of the pellet samples was determined using a Retsch Technology Camsizer® (Jenoptik, Haan, Germany). Approximately 30 g of the yield for each batch were analyzed in triplicate. The roundness of the pellets was calculated using the following equation:

$$\text{roundness} = \frac{4\pi A}{P^2} \quad (2)$$

where A is the area occupied by a single pellet image, and P is its perimeter. The two-dimensional image of a sphere has a roundness of 1. Any other shape has a roundness less than 1.

The internal and external morphologies of the pellets were investigated using a Model S-530 scanning electron microscope (SEM) (Hitachi, Tokyo, Japan) at 10 kV. Pellets were mounted on aluminum studs as a whole pellet, or after being sliced in half, and then sputtercoated with gold for approximately 1 min. The images of the pellets were viewed at 50× magnification.

Release studies were performed using a Model 2100 USP dissolution apparatus II (Distek, Somerset, NJ). Pellet samples were consistently 800 mg. The release medium was 0.05 M phosphate buffer at pH 6.8 maintained at 37.0 ± 0.1 °C. Samples were withdrawn at predetermined time points and analyzed at 288 nm using the UV–visible spectrophotometer. All studies were performed in triplicate. The drug released as a function of time was expressed as the propranolol mass released.

To examine the effect of calcium on drug release, release studies were performed in the same manner described in drug release studies. The concentration of calcium was measured using a calcium specific electrode (Denver Instrument, Denver, CO). The 1000 ppm calcium individual certified cation standard was used in all standard solution preparations.

Preliminary studies revealed that propranolol interfered with the calcium measurement. To account for this interference, 1 ml of corresponding propranolol solutions was added to 50 ml of individual calcium standard solutions such that each standard solution contained a propranolol concentration equivalent to that of 100% drug released, as obtained in drug release studies. Furthermore, 1 ml of 1 M potassium chloride solution was added to each 50 ml solution as the ionic strength adjuster, as suggested by the manufacturer. Because it is difficult to measure calcium at very low concentrations, 1 ml of 70 ppm calcium solution was added to each 50 ml of standard solution. At 5, 15, 30, and 60 min in the calcium release study, a 50 ml sample was withdrawn and replaced with an equal volume of 37 °C release medium. A 1 ml aliquot of 1 M potassium chloride solution, 1 ml of 70 ppm calcium solution, and 1 ml of corresponding propranolol solution were added to individual sample solutions. All measurements were performed at room temperature and in triplicate.

2.7. Data analysis and model fitting

Statistical analysis was performed using SigmaStat version 3.1 (Systat Software, Inc., San Jose, CA). A p-value less than 0.05 indicates significance.

To gain insight into the contributions to the release mechanism, four release models were fit to the drug release data.

Model I

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} \quad (4)$$

Model I acknowledges that Fickian diffusion of dissolved drug through an essentially intact pellet matrix is the only release mechanism involved (Higuchi, 1963). M_t/M_∞ represents the fraction of the drug released, k_1 is the diffusion constant, and t is release time. Only 80% of the release data was used to fit the equation to the data (Bommareddy et al., 2006; Paker-Leggs and Neau, 2008).

Model II

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} + k_2 t \quad (5)$$

In Model II, polymer relaxation, involving hydration and swelling, was acknowledged in the $k_2 t$ term as an additional contribution to the release mechanism (Harland et al., 1988). Only 90% released data was used in the model fitting (Bommareddy et al., 2006; Paker-Leggs and Neau, 2008).

Model III

$$\frac{M_t}{M_\infty} = k_1 t^m \quad (6)$$

In Model III, instead of m being fixed to 0.5 as in Model I, the best-fit values for m were investigated (Ritger and Peppas, 1987). If m is 0.5, the release mechanism is strictly diffusion. If m is between 0.5 and 1, then there is non-Fickian diffusion or, more likely, a release mechanism in addition to Fickian diffusion is involved. Only 90% released data was used to fit the model to the data (Ritger and Peppas, 1987).

Model IV

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \quad (7)$$

In this model, the exponent for the polymer relaxation term, $k_2 t^{2m}$, was expected to be twice that found in the diffusion term, $k_1 t^m$ (Peppas and Sahlin, 1989). Only 90% released data was used in the model fitting process (Bommareddy et al., 2006; Paker-Leggs and Neau, 2008).

Using the sum of the squared residuals (SSR), the number of data pairs (n), and the number of estimable parameters (p), the Akaike Information Criterion (AIC) will be calculated in order to find the best fit model with the fewest number of estimable parameters (Yamaoka et al., 1978):

$$\mathrm{AIC} = n[\ln(\mathrm{SSR})] + 2p \quad (8)$$

A more negative AIC value indicates a better fitting model.

3. Results

DSC studies revealed that the purities of PF and PM were 99.4 ± 0.1%, and 96.5 ± 0.6%, respectively. The melting point for PF was 91.9 ± 0.2 °C, which confirmed the identity of the free base since a published melting point for propranolol free base with a purity of 99.2% was 92.9 °C (Neau et al., 1993). In order to backcalculate the purity of the propranolol forms, standard curves were established, and UV analysis was performed. The purity of PF and PM was 99.0 ± 2.9% and 100.2 ± 1.3% when taking the purity of PH as the standard.

Complexation studies revealed that, although the precipitated mass for hydrochloride and free base forms were comparable, the maleate provided the least amount of precipitate (Fig. 2). The difference between the precipitated mass for PM and the others became larger as the drug concentration increased, indicating the potential for an increase in the difference in precipitate mass *in situ* in the drug release study as the drug concentrations are expected to be higher in the gel layer than in the complexation study.

The moisture content of each pellet product was less than 1%, and masses were consistent at the 10 and 15 min time points, indicating that available moisture was essentially completely lost by 10 min. Although Avicel can hold much water as bound water that is not readily evaporated (Agrawal et al., 2004), the comparable moisture content and the reasonably consistent Avicel content in the different batches indicate that no batch discouraged release medium entry to a greater degree due to a higher moisture level in the pellets.

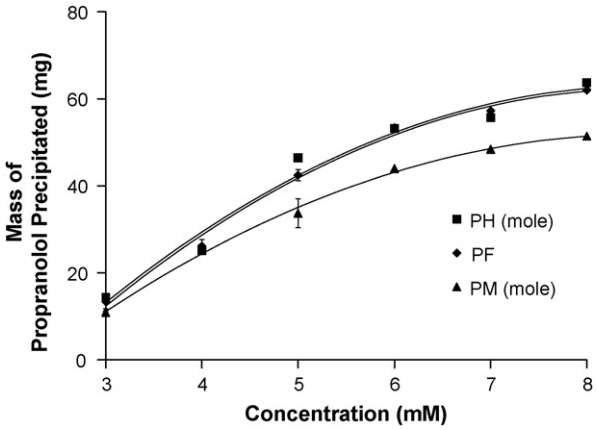

Fig. 2. Precipitated masses for the three propranolol forms. The data points with triangles present results for PH (mole), the diamonds present results for PF, the squares present results for PM (mole). Note that the curves are not theoretical, nor predictive, but rather reveal data trends.

Sieve analysis revealed that the highest yield (Table 1) was obtained with the formulation containing the fixed moles of PH (Kruskal Wallis One-Way Analysis of Variance on Ranks (KWA) (De Muth, 1999), followed by the Student Newman Keul method (SNK) ($p \leq 0.007$)). Changing the moles of the drug form to the corresponding mass in the formulations did not change the yield significantly (KWA, followed by SNK, $p \geq 0.05$). The average pellet diameters (Table 1) when the moles of the drug forms were fixed were comparable, and changing the moles of the drug form to mass in the formulations did not change this result significantly (KWA, followed by SNK, $p > 0.05$).

The friability results are presented in Table 1. It is apparent that the friability values for the PM batches are lower than the others, indicating that the PM beads are more rugged. Indeed, the PM friability results are statistically different from those of the PH and PF batches ($p < 0.001$). The effect on friability of an increase in the content of either of the salt forms in the wetted mass was minimal.

Formulations where PM was fixed as mass and moles provided the roughest surfaces as explored by SEM analysis (Fig. 3). The images of the interior of the pellets revealed similar textures. Roundness tests confirmed that PM pellets were the least round (Table 1), and were different from the others (one-way ANOVA, followed by SNK, $p < 0.02$).

The amount of calcium released was essentially comparable (KWA, $p > 0.05$) at any time point for all of the batches (Fig. 4) with the sole exception of the 30 min data for the PH (mass) batch

Table 1
Yield, average diameter, roundness, and friability results for the different propranolol form batches.

Drug form (fixed as mole or mass in the formulation)	% Yield	Avg. diameter (mm)	Roundness	Friability %
PF (mass and mole)	85.9 ± 1.0	1.00 ± 0.01	0.97 ± <0.01	2.0 ± 0.08
PH (mole)	75.3 ± 1.1	0.99 ± 0.02	0.97 ± <0.01	2.0 ± 0.2
PM (mole)	80.1 ± 1.8	1.07 ± 0.02	0.96 ± <0.01	0.8 ± 0.24
PH (mass)	77.7 ± 1.7	1.07 ± 0.02	0.97 ± <0.01	2.9 ± 0.12
PM (mass)	80.9 ± 1.6	1.14 ± 0.02	0.96 ± <0.01	0.4 ± 0.18

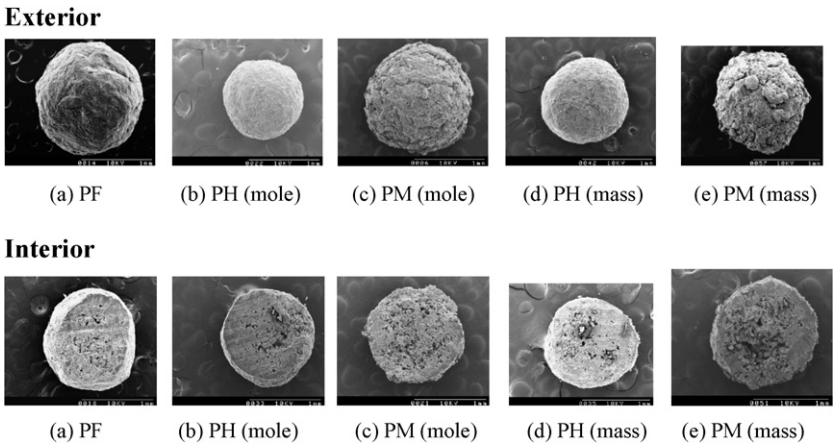

Fig. 3. Scanning electron microscopy analysis: exterior surfaces and interiors of the pellets.

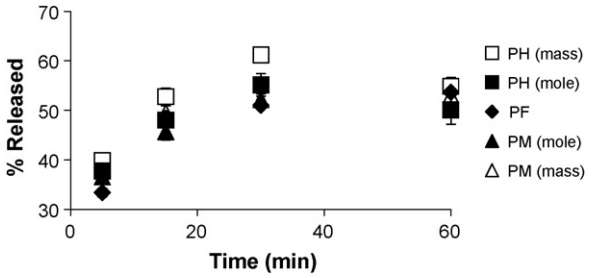

Fig. 4. Released calcium as a function of time from propranolol (mole) and (mass) batches.

where calcium released was greater than observed with the other batches (one-way ANOVA, followed by SNK, $p < 0.006$). Calcium release reached a plateau after 30 min for the PF (KWA, followed by SNK, $p > 0.05$) and PM (mole) pellets (one-way ANOVA, followed by SNK, $p > 0.05$). On the other hand, in the case of PH (mole), PH (mass), and PM (mass) batches, the calcium released reached a plateau after 15 min (one-way ANOVA, followed by SNK, $p > 0.05$).

The microenvironmental pH study revealed that the pH values for each of the batches (Fig. 5) were not significantly different from each other up to 8 min (one-way ANOVA, $p > 0.05$). After 8 min, data points for the PF formulation were significantly different from the other data (one-way ANOVA, followed by SNK, $p < 0.001$).

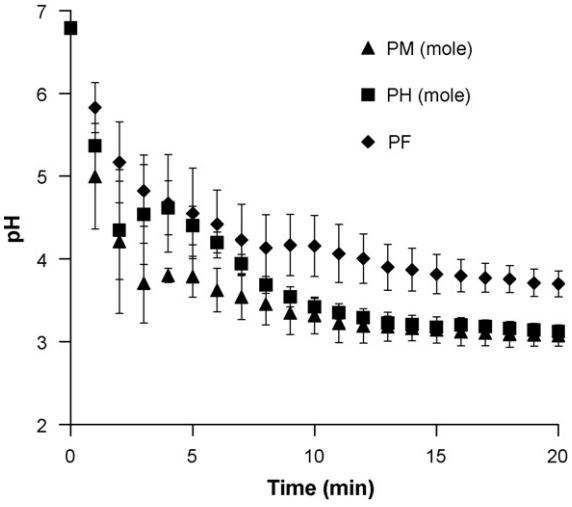

Fig. 5. Microenvironmental pH study results for propranolol (mole) batches.

Pellets containing PF provided the slowest release (Fig. 6a). PM (mole) batches (Fig. 6b) and PH (mole) batches (Fig. 6c) revealed a faster release than PM (mass) and PH (mass), respectively. Mathematical modeling for the first three models is presented in Table 2.

Table 2
Parameter values from model fitting to the release data and the assessment of the fit for each type of pellet sample.

Propranolol form	$k_1 \pm$ std error	$k_2 \pm$ std error	$m \pm$ std error	r^2	SSR	AIC
Model I						
PF	0.0984 ± 0.008	–	–	0.857	0.0366	−17.85
PH (mole)	0.114 ± 0.007	–	–	0.903	0.0285	−19.35
PM (mole)	0.116 ± 0.005	–	–	0.949	0.0124	−24.34
PH (mass)	0.112 ± 0.008	–	–	0.881	0.0201	−17.54
PM (mass)	0.125 ± 0.005	–	–	0.950	0.00762	−22.38
Model II						
PF	0.0248 ± 0.0015	0.0145 ± 0.0003	–	0.999	0.000063	−54.03
PH (mole)	0.0520 ± 0.0099	0.0122 ± 0.0019	–	0.991	0.00251	−31.92
PM (mole)	0.0745 ± 0.0061	0.00814 ± 0.0011	–	0.996	0.000972	−37.62
PH (mass)	0.0575 ± 0.010	0.0118 ± 0.002	–	0.990	0.00295	−30.96
PM (mass)	0.0934 ± 0.0085	0.00687 ± 0.0016	–	0.993	0.00188	−33.66
Model III						
PF	0.0306 ± 0.001	–	0.862 ± 0.013	0.999	0.000160	−48.44
PH (mole)	0.0504 ± 0.006	–	0.754 ± 0.034	0.995	0.00157	−34.74
PM (mole)	0.0684 ± 0.004	–	0.664 ± 0.017	0.998	0.000457	−42.14
PH (mass)	0.0546 ± 0.007	–	0.738 ± 0.036	0.994	0.00189	−33.63
PM (mass)	0.0857 ± 0.007	–	0.626 ± 0.024	0.996	0.00113	−36.71

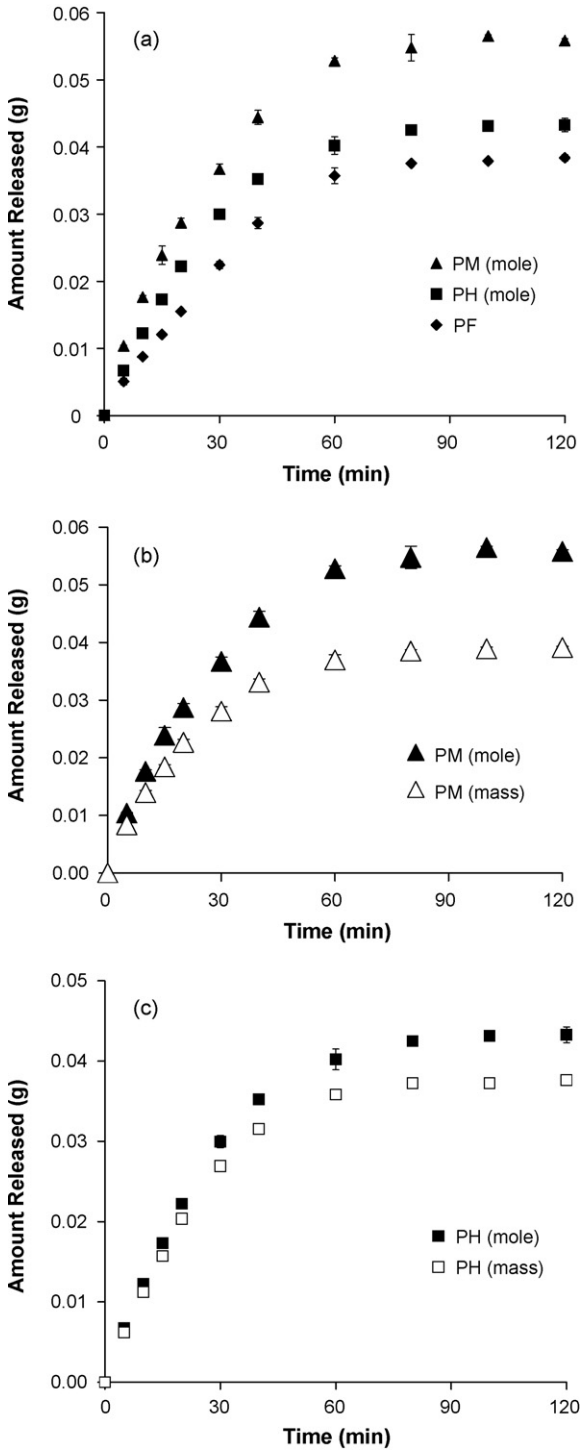

Fig. 6. (a) Released amount of drug as a function of time for propranolol (mole) batches. (b) Released amount of drug as a function of time for PM (mole) and PM (mass) batches. (c) Released amount of drug as a function of time for PH (mole) and PH (mass) batches.

When using Model IV (data not shown), k_1 approximated zero, except in the case of the PF batch. The similarity of the k_2 and $2m$ of Model IV to k_1 and m of Model III, respectively, reveals that Model IV has collapsed to Model III. In the case of the PF batch, Model IV was not a good fit and the significance of the estimated parameters was not supported, as indicated by their p values. Judging by the AIC value, Model II provides the best fit to the PF data.

4. Discussion

It is interesting that, when the drug forms were fixed as moles in the formulations, PM revealed a faster release rate than PH, and PF revealed the slowest release profile. On the other hand, when the content of the salt forms were decreased to an amount equivalent to that found in the PF batch, e.g. PH (mole) to PH (mass), the drug release rate decreased as expected due to a lower concentration gradient effect. The expected influences at the moving front, in the hydration and dissolution layer, as well as in the gel layer, will be discussed below.

4.1. At the moving front and in the hydration and dissolution layer

Microenvironmental pH studies demonstrated that the pH started decreasing immediately after the addition of the pellets to the vials (Fig. 5). Since the pH dropped in every case, this revealed that protons released by hydrated Carbopol molecules would dominate the pH effects at the moving front and in the hydration and dissolution layer in each case.

Although it was not significant, the pH values decreased more initially in the case of PM (mole) pellets. The implication is that, when there is less release medium present at the moving front and in the hydration and dissolution layer, as there would be in the release studies, deprotonation of maleate ions to form divalent maleate might result in a greater decrease in pH that could significantly lower the microenvironmental pH, leading to a more tortuous pathway by the discouragement of the swelling of Carbopol, thus sustaining drug release (Paker-Leggs and Neau, 2008). However, the fact that propranolol release was fastest from the PM (mole) batch (Fig. 6) implies that this tortuosity was not profound enough or was of insufficient duration to make a difference in the overall release rate. Such a phenomenon would not be expected to occur with PH batches, since there would be a minimal contribution to the microenvironmental pH by this form.

On the other hand, the presence of monovalent and divalent maleate molecules would have interfered with the interaction between protonated propranolol and carboxylate groups of Carbopol, leading to a faster diffusion of the drug through the hydration and dissolution layer. This effect would have been less profound for PH than for PM batches, since the contribution of chloride ions to the ionic strength would be less than expected from divalent maleate and the overall interference would be correspondingly less. The difference in degrees of interference with this interaction was likely one of the reasons that the release of PH was slower than that of PM.

It appears that solubility was not a determining factor in the overall drug release rates of PM and PH forms. The lower solubility of PM might have been compensated by the common ion effect of chloride ions provided by calcium chloride that would reduce the solubility of PH (Thomas and Rubino, 1996) and its subsequent dissolution rate in the penetrating release medium.

The PF batch does not experience this ionic interference due to the drug form, but an increase in pH in comparison to the other two forms is evident (Fig. 5). This increase in pH is again likely to be more influential in the release studies and would lead to an opening of the matrix as the Carbopol swells in the hydration and dissolution layer. PF should be released faster than the other two forms due to this microenvironmental pH effect generating a less tortuous pathway for drug diffusion (Paker-Leggs and Neau, 2008). However, the fact that PF provided the slowest drug release rate (Fig. 6) implies that this effect was not great enough to make a profound difference in the overall release rate. The difference in the pH values between the PF batch and those of the other two forms became significant ($p < 0.001$) after 8 min, probably due to the slow but eventual

dissolution of PF, which suggests that the low solubility of PF might have limited its contribution to the microenvironmental pH at the moving front and in the hydration and dissolution layer.

The results of the drug release studies therefore indicate that the different contributions to the microenvironmental pH by the different propranolol forms are of little consequence to the drug release rate. The contribution of the interference of the propranolol–Carbopol interaction by the drug counterion, on the other hand, is supported by the relative drug release rates.

When the release profiles of the PM (mole) and (mass) batches as well as the PH (mole) and (mass) batches are compared, in both cases decreasing the drug amount in the formulations decreases the release rate (Fig. 6b and c, respectively), suggesting that release was at least in part concentration gradient driven and dissolved drug diffusion is a release mechanism. A decrease in the amount of these salts of propranolol demonstrated a drug loading effect (Kim et al., 1992), evidenced by a decrease in the drug release rate.

4.2. In the gel layer

The precipitation brought about by PM solutions was less than observed with the other two forms (Fig. 2), which implies that the presence of monovalent and divalent maleate molecules successfully interfered with the interaction between protonated propranolol and carboxylate groups of Carbopol. This interference would have encouraged the drug molecules to diffuse faster through the gel layer. Therefore, the enhanced ionic strength in the gel layer was also likely a reason why the drug was released even faster from PM (mole) pellets than from PM (mass) pellets.

The effect of ionic strength on the gel layer thickness should also be considered. Nakanishi et al. (1998) suggested that an increase in ionic strength would affect the thickness of the gel layer, resulting in a decrease in the diffusion pathlength for the drug. The thickness of the gel layer, then, should be the least for PM (mole) and the most for PF pellets. This difference in the diffusion pathlength would result in the fastest release for PM (mole) pellets and the slowest for PF pellets. This is confirmed in the release profiles, suggesting that gel thickness could be a contributing factor to drug release rates.

4.3. Effect of calcium on drug release

Because calcium chloride is a strong electrolyte, once the release medium penetrates, it would immediately dissolve and calcium and chloride ions can contribute to the ionic strength in each of the formulations. Dissolved calcium ions are available to interact with the carboxylate groups of Carbopol in the hydration and dissolution layer. This would have a negative influence on the gelling of Carbopol (Charman et al., 1991; Gomez-Carracedo et al., 2001). Since PF encourages gel formation even in the hydration and dissolution layer, the presence of dissolved calcium ions would lead to a more tortuous pathway for drug diffusion. The overall ionic strength influence, however, would be the least pronounced in the PF batches in the hydration and dissolution layer and in the gel layer, because of the absence of miscellaneous ions in the drug form (Kriwet and Kissel, 1996).

In the case of PM, monovalent and divalent maleate should interact with calcium ions at least as effectively as the carboxylate groups of Carbopol. Encouraged deprotonation of Carbopol and the presence of more maleate ions might have been the reasons that the time to reach the calcium plateau extended to 30 min for PF and PM (mole) batches, respectively, since in both cases carboxylate groups are more available to form insoluble or poorly soluble calcium salts. On the other hand, the association of calcium ions with maleate molecules or with carboxylate groups of Carbopol would influence the diffusion of protonated propranolol adversely or beneficially, respectively.

It is interesting that the calcium ions did not release completely (Fig. 4). Kriwet and Kissel (1996) reported calcium complex formation with a low crosslinked poly(acrylic acid), viz. Noveon® Polycarbophil AA-1, when that polymer is neutralized. Carbopol® 974P in the present study is a highly crosslinked poly(acrylic acid). Formation of insoluble maleate or Carbopol salts of calcium in the hydration and dissolution layer and in the gel layer could account for incomplete calcium release.

4.4. Characterization and drug release studies

Although the batch with PF provided the highest yield ($p < 0.002$, Table 1), this is contrary to what was reported in a previous study (Paker-Leggs and Neau, 2008) where, although the powder blend was the same, the wet massing fluid contained one-third the amount of calcium chloride, resulting in a tackier wetted mass. In the present study, there was no indication of tack during the manufacture of the PF batch. Therefore, the high yield of the PF batch can be attributed to the higher calcium chloride content. The greater number of calcium ions would associate with more carboxylate groups of Carbopol in the wetted mass, which would reduce both the tack and the gelation, resulting in a lower quantity of water in the gel region (Gomez-Carracedo et al., 2001, 2007). The extrudates would be denser and therefore undergo less densification than observed in the previous study. The yield for PH (mole) and PM (mole) batches were significantly different ($p < 0.019$). The PH (mole) batch had the lowest yield. PM provided higher yields because monovalent maleate would discourage Carbopol gel formation even further than calcium chloride alone would, which would result in a greater density of the wetted mass that would allow less shrinkage during spheronization than PH wetted mass batches would.

Statistical analysis revealed that the average pellet diameters of the batches (Table 1) were not significantly different from each other ($p > 0.05$). This indicates that the interference with the gel formation of Carbopol and different Avicel amounts in the wetted mass do not have a significant effect, or have compensating effects, on the average pellet size.

Roundness scores (Table 1) and SEM images (Fig. 3) revealed another response different from a previous study (Paker-Leggs and Neau, 2008). In the present study, the pellets of PH (mole) and PH (mass) batches had roundness scores and smoothness comparable to that of the PF batch pellets ($p > 0.05$). This is not surprising since, in the present study, the calcium amount employed in the wetting fluid was three times the amount used in the previous study. It is well established that calcium ions associate with the carboxylate groups of Carbopol, reduce the tack, and consequently improve pellet roundness (Neau et al., 1996). The PM (mass) and PM (mole) pellets that had rougher surfaces would experience successful maleate competition for calcium ions and this would lead to reduced calcium associations with carboxylates of Carbopol and less round pellets. The acidic nature of maleate would discourage Carbopol deprotonation and calcium ions would have fewer carboxylates with which to associate. This pH effect was also evident in the previous study (Paker-Leggs and Neau, 2008), where the wetted mass of the propranolol maleate formulation demonstrated the least tack in the absence of calcium chloride in the force of detachment studies and yet their pellets had the roughest surfaces. The availability of calcium ions to Carbopol and Carbopol deprotonation in the wetted mass appear to be the two factors that most profoundly affect the pellet roundness and smoothness.

Although rough surfaces of PM mole and mass pellets would provide more surface area for initial release medium entrance into

the pellets during the release studies, this should not influence the drug release rate markedly. As suggested by Huber and Christenson (1968), once the gel layer forms, the somewhat different surface areas should become comparable.

The friability results reveal much about the effect of the drug form and the effect of calcium on the ruggedness of the beads. It is evident that the maleate salt form has the most profound effect on providing a rugged bead (Table 1). This is believed to be due to the ability of monovalent and divalent maleate to bind with calcium ions and thus interfere with the calcium interaction with the carboxylates of Carbopol. When the carboxylates of Carbopol are free, they can impart ruggedness to the bead. In fact, it is reported that, because of its binding effect (Funck et al., 1991), as little as 2% Carbopol can reduce the friability in pellet formulations containing 18% Avicel PH101. This effect is not observed with the PF and PH results because these forms of the drug do not interfere markedly with the calcium interaction with Carbopol carboxylates. The minimal effect on friability of the level of the salt form of the drug in the formulation is understandable since the drug accounts for only 5–7.24% of the formulations.

Data analysis revealed that r^2 values were high and AIC values were low for the fit of Model II, as well as Model III, to the drug release data. The m value substantially higher than 0.5, observed with the fit of Model III, indicates that a mechanism other than dissolved drug diffusion through the pellet matrix is likely. The fact that Model II also fits the data well suggests that polymer relaxation was contributing to the drug release mechanism. Based on the equation below, the fraction of the drug released by the diffusion mechanism can be estimated as a function of release time (Peppas and Sahlin, 1989). Instead of using the estimated parameters from the fit of Model IV to the data, as intended by Peppas and Sahlin, m was fixed at 0.5 and the k_1 and k_2 came from the fit of Model II because the fit of Model IV was questioned, as described above.

$$F = \frac{1}{1 + k_2/k_1 t^m} \tag{9}$$

Fig. 7 reveals how the fractional diffusion changed with time for pellets involving the three drug forms with the same mole content. It is evident that, for the PF pellets, polymer relaxation had a greater influence on drug release, which might account for the better fit of Model II rather than Model III to the data. This is not surprising since PF encourages Carbopol relaxation that would include hydration, swelling, and gelling of the polymer (Sudipto et al., 2002). In the case of the salt form batches, increasing the drug content should increase the initial release medium entry rate by making the surface more hydrophilic. It should be noted that k_2 increased and k_1 decreased in Table 2, in going from mass to moles in Model II for a particular salt form, which indicates polymer relaxation is more likely and takes place faster with the higher moles of the salt forms in PH (mole) and PM (mole) batches.

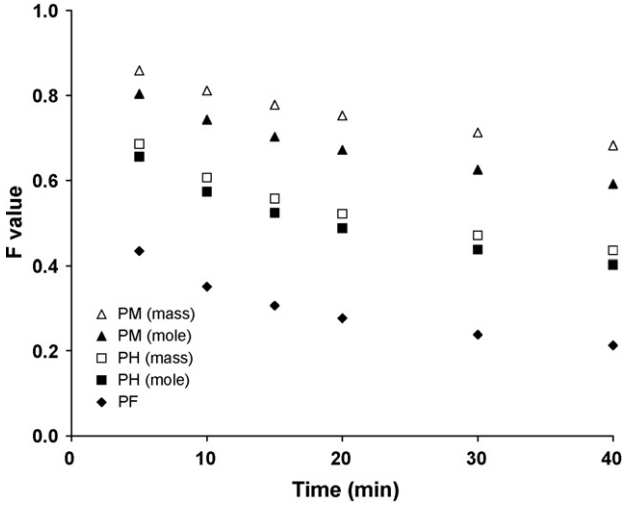

Fig. 7. The fraction of drug released by Fickian diffusion as a function of time from each type of pellet sample.

5. Conclusion

When the drug content in the pellet formulations was fixed at a certain number of moles, employing different forms of propranolol still resulted in different yields, roundness scores, and release rates. However, average pellet diameter did not change.

Although the release rate decreased when the amounts of the salt forms were decreased from moles to mass in the formulations, comparable yield, average diameter, and roundness scores were obtained. The different pellet formulations revealed comparable calcium release rates. Fickian diffusion and polymer relaxation were contributing release mechanisms for each batch of pellets.

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